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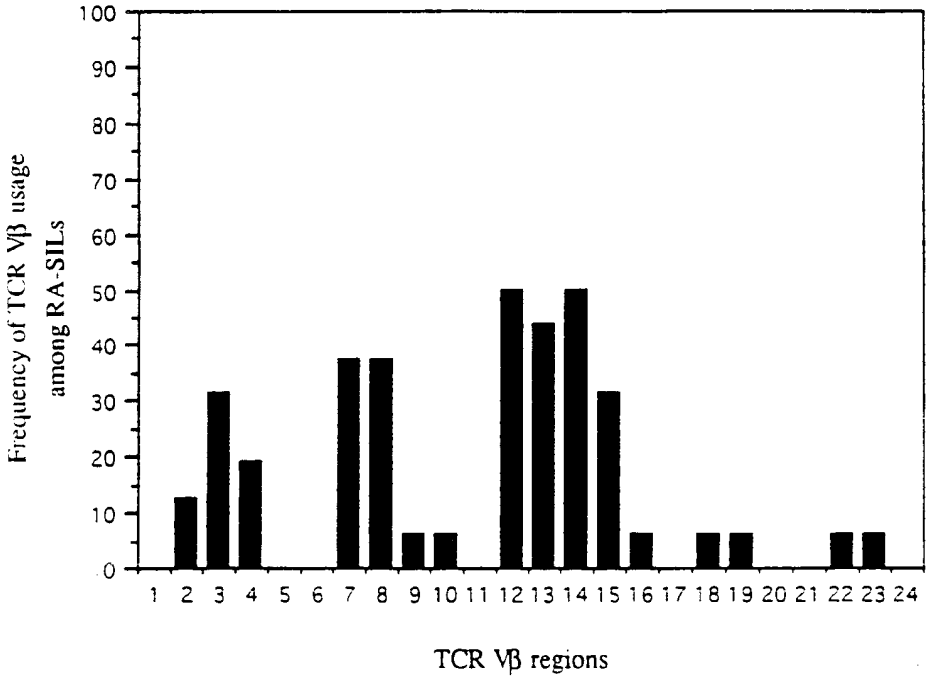

(57) Abstract

Rheumatoid arthritis patients preferentially use the T-cell receptor domains $V_\beta 14$, $V_\beta 7$, $V_\beta 8$, $V_\beta 12$, $V_\beta 13$, $V_\beta 15$, $V_\beta 2.2$, $V_\beta 2.3$, $J_\beta 2.1$, $J_\beta 2.5$, $J_\beta 2.7$, and $C_\beta 2$. Patients are treated with polypeptides containing sequences from these domains or with antibodies capable of specifically binding these domains. Improved methods for diagnosing V_β usage in autoimmune disease are provided. The use of J_β polypeptides and antibodies for the treatment of autoimmune disorders is new.

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DIAGNOSING AND TREATING AUTOIMMUNE DISORDERS

Background of the Invention

This invention relates to autoimmune diseases. In particular, it relates to methods for treating rheumatoid arthritis and for diagnosing and treating autoimmune disorders.

Autoimmune disorders are characterized by an immune attack mounted against one or more self antigens. They include arthritis (osteo- or rheumatoid), Issac's syndrome, psoriasis, insulin dependent diabetes mellitus, multiple sclerosis, sclerosing panencephalitis, systemic lupus erythematosus, Sjögren's syndrome, rheumatic fever, ankylosing spondylitis, Reiter's disease, inflammatory bowel disease (including ulcerative colitis and Crohn's disease), Guillain-Barré-Strohl syndrome, primary biliary cirrhosis, chronic active hepatitis, glomerulonephritis, myasthenia gravis, pemphigus vulgaris and Graves' disease. This invention is especially concerned with T cell-mediated autoimmune disorders, i.e. chronic autoimmune responses in which T-cells are primarily involved in the direct immune response (in contrast to such disorders as some forms of glomerulonephritis which primarily result from the generation of excessive amounts of antibody-antigen complexes). Of particular interest are myasthenia gravis, inflammatory bowel disease, insulin dependent diabetes mellitus and rheumatoid arthritis.

Rheumatoid arthritis (RA) is a chronic heterogeneous disorder in which a variety of etiological agents may be responsible for initiating a series of events leading to inflammation in multiple joints. The cause of the disease remains unknown, although by analogy with other forms of arthritis such as that accompanying Lyme disease, it has been postulated that infection with as yet unidentified bacteria or viruses in a genetically susceptible host is an initiating event. Persistence could result from the presence of viral or bacterial antigens that generate an immune response or cross-react with host tissues together with amplification effects of cellular products of the host.

While many patients have systemic manifestations in RA, many of the most serious consequences of RA stem from its effects on articular connective tissues, which are characterized by alterations of the synovial membrane with proliferation of lining cells and infiltration by chronic inflammatory cells. Erosions of bone occur in areas contiguous with the inflammatory cell mass as well as in regions adjacent to bone marrow distant from the inflammation. The bone erosions are probably produced through induction of differentiation and activation of osteoclast progenitors. The erosion of soft connective tissues, e.g., cartilage, joint capsules, tendons, and ligaments, results from direct release of proteolytic enzymes from cells of the inflammatory cell mass or from polymorphonuclear leukocytes that are typically abundant in rheumatoid synovial fluids, although rare in the synovial membrane. See, for example, Harris, in W. N. Kelley et al., eds., Textbook of Rheumatology, W.B. Saunders, Philadelphia, pp. 886-915 (1985); Dayer and Krane, Clin. Rheum. Dis., 4: 517-

537 (1978); Krane, in Arthritis and Allied Conditions. A textbook of Rheumatology, ed. by D.J. McCarty, pp. 593-604, Lea and Febiger, Philadelphia (1985); and Krane et al., Lymphokines, 7: 75-136 (1982).

The major macromolecules contributing to the structural integrity of the extracellular matrix are the interstitial collagens. Other matrix components include glycoproteins and proteoglycans. Degradation of articular cartilage could not only result from release of proteases from cells (synovial fibroblasts and monocyte/macrophages) outside the cartilage, but chondrocytes within the cartilage may be induced to degrade their own matrix. This process is relevant not only to rheumatoid arthritis, but also to polychondritis and osteoarthritis. Human mononuclear phagocytes release relatively little collagenase, but these cells contribute to matrix degradation by producing other enzymes, such as elastase, as well as active oxygen species. The major contribution of monocytes/macrophages to tissue destruction is likely to be due to the release of cytokines that stimulate synovial fibroblasts to secrete metalloproteinases. In turn, lymphocytes infiltrating the synovium release factors that stimulate macrophages to produce their cytokines as well as have a direct effect on fibroblasts. Thus, lymphocytes directly or indirectly can stimulate synovial fibroblasts to produce enzymes that destroy joint tissue.

In the first stage of RA, mononuclear phagocytes are drawn into the rheumatoid synovial tissue and release IL-1 in response to the early inflammatory response to activation of the immune system. IL-1 and other growth/activation factors, including TNF/cachectin, stimulate proliferation of the synovial cells and induce biosynthesis of prostaglandins and proteinases by the synovial cells. Adherent synovial cells respond by mitogenesis to factors that do not stimulate production of prostaglandins and/or proteinases. Synovial cells exposed to IL-1 react with a battery of responses, including the expression of prostaglandins, metalloproteinases, the proto-oncogene products fos and jun, and melanoma growth stimulatory activity (MGSA).

The responses of synovial cells to IL-1 are modified by the action of other lymphokines and monokines such as TNF-α and TNF-β, produced by the inflammatory cells. The cytokines act primarily through cell surface receptors to activate transcription of the procollagenase gene, probably mediated by complexes of nuclear oncoproteins.

The persistence of the inflammatory response is mediated by T lymphocytes that are present at the disease site. Activated T lymphocytes are present in rheumatoid synovial tissue and frequently are found adjacent to macrophages. Clonal dominance of T lymphocytes has been observed using Southern blot analysis of DNA obtained from synovial T-cells of patients with rheumatoid arthritis (Stamenkovic et al., Proc. Natl. Acad. Sci. 85:1179-1183 [1988]).

Therapy for RA depends on the stage of the disease. Stage 1, where a postulated antigen is presented to T-cells with no obvious arthritic symptoms, is not treated. Stage 2

involves T-cell and B-cell proliferation and angiogenesis in synovial membrane, resulting in malaise, mild joint stiffness, and swelling. During Stage 3, neutrophils accumulate in synovial fluid and synovial cells proliferate without polarization or invasion of cartilage, resulting in joint pain and swelling, morning stiffness, malaise, and weakness. Current therapy for Stages 2 and 3 includes bed rest, application of heat, supplemental icosapentaenoic and docosahexanoic acid, and drugs.

Nonsteroidal anti-inflammatory drugs, including aspirin, continue to be the foundation of drug therapy in treating Stages 2 and 3 of the disease. Those anti-inflammatory drugs other than aspirin include indomethacin, phenylbutazone, phenylacetic acid derivatives such as ibuprofen and fenoprofen, naphthalene acetic acids (naproxen), pyrrolealkanoic acid (tometin), indoleacetic acids (sulindac), halogenated anthranilic acid (meclofenamate sodium), piroxicam, zomepirac, and diflunisal.

Second-line drugs for RA Stages 2 and 3 include anti-malarial drugs such as hydroxychloroquine, sulfasalazine, gold salts, and penicillamine, and low-dose methotrexate. These alternatives frequently produce severe side effects, including retinal lesions and kidney and bone marrow toxicity.

The irreversible destruction of cartilage occurs in Stage 4 of the disease. Currently available drugs and treatments include total lymphoid irradiation, high-dose intravenous methylprednisolone, and cyclosporine. Cyclosporine is nephrotoxic and the other treatments exert substantial toxicity as well. As a result, such immunosuppressive agents heretofore have been used only in the treatment of severe and unremitting RA.

Other possible therapeutic drugs for Stage 4 of RA include cyclic oligosaccharides (cyclodextrins), which, when combined with a noninflammatory steroid (cortexolone), inhibit angiogenesis *in vivo*. Folkman et al., Science, 243: 1490-1493 (1989). Antibodies against crucial components of the early phase of the immune response include anti-Class II MHC antibodies [Gaston et al., Arthritis Rheum., 31: 21-30 (1988); Sany et al., Arthritis Rheum., 25: 17-24 (1982)], anti-interleukin-2 receptor antibodies [Kyle et al., Ann. Rheum. Dis., 48: 428-429 (1989)], anti-CD4 antibodies [Herzog et al., J. Autoimmun., 2: 627-642 (1989); Walker et al., J. Autoimmun., 2: 643-649 (1989)], and antithymocyte globulin [Shmerling and Trentham, Arthritis Rheum., 32: 1495-1496 (1989)]. The last three of these drugs have been used successfully in patients with RA.

Cytokines or their inhibitors have properties that could down-regulate inflammatory and proliferative pathways in RA. For example, transforming growth factor-β (TGF-β) suppresses induction of procollagenase by certain growth factors but augments the effects of these growth factors on TIMP. Edwards et al., EMBO J., 6: 1899-1904 (1987). See also Ignotz and Massague, J. Biol. Chem., 261: 4337-4345 (1986); Wahl et al., J. Immunol., 140: 3026-3032 (1988); Gamble and Vadas, Science, 242: 97-99 (1988); U.S. Pat. No. 4,806,523

issued Feb. 21, 1989; EP 269,408 published June 1, 1988. Others have tested inhibitors of interleukin-1 [Herzog et al., Concepts Immunopathol., 7: 79-105 (1989)], platelet-derived growth factor [Bonin and Singh, J. Biol. Chem., 263: 11052-11055 (1988)], and interferon-gamma [Amento and Hayes, Clinical Res., 36: 599A (1988)] with limited success. Synovectomy by irradiation with macroaggregates of ferric hydroxide labeled with a short-lived isotope (dysprosium-165) has also been attempted. Sledge et al., Arthritis Rheum., 29: 153-159 (1986); Vella et al., Arthritis Rheum., 31: 789-792 (1988).

By the time RA reaches Stage 5, irreversible destruction of cartilage is well underway. Aggressive therapy with cytotoxic drugs may not be effective at this point. Systemic vasculitis in patients with Stage 5 disease must be treated with glucocorticoids, cytotoxic drugs, or both, but in other than life-threatening situations, physical therapy and reconstructive joint surgery give the best functional results.

The T-Cell Receptor (TCR) is a glycoprotein with a molecular weight of 89 to 90 kdal. It is a dimer consisting of one alpha polypeptide chain and one beta polypeptide chain, each about 40 to 50 kdal, linked by disulfide and noncovalent bonds. In addition, two more TCR chains have been identified, the gamma and delta chains. The TCR exhibits structural and amino acid sequence homology with immunoglobulins. Each TCR chain contains, in N- to C-terminal order, a leader sequence, a variable domain (made up of at least V and J sequences), a constant domain, a transmembrane sequence, and an endoplasmic domain. The genome contains a multiplicity of V, D, and J segments that must be assembled by DNA recombination to produce a particular TCR. This assembly occurs during thymic development of the T-cell repertoire, at least for alpha and beta chains. As a result, a clone or group of T-cells will bear the same TCR, and this clone or group will be found in the presence of a number of other clones bearing differently rearranged TCR. There are approximately 24 presently known families of the TCR beta chain V region, each family consisting of a number of alleles of a distinctive V domain (there are over 40 such alleles embraced within the 24 presently known families). Beta chain V region families are henceforth designated $V_\beta X$, where X is the family designation. The joining or "J" domains of the beta chains are grouped into 2 large classes, 1 and 2, and these in turn are subdivided between them into about 14 presently known families. Finally, 2 classes of beta chain constant domains of have been identified.

Attempts have been made to correlate the presence of a particular TCR family with various disorders. Davies et al. have reported that the TCR V_α domain of intrathyroidal T-cells in autoimmune thyroid disease is highly restricted, with V_α gene family 15 being proportionately over-represented in the intrathyroidal accumulation ("New England J. Medicine," 325 (4):238-244 [1991]). It is also known that $V_\beta 8$ genes (note that the beta chains of more than one species bearing the same numerical designations should not be assumed to be homologous) are preferentially used by encephalitogenic T-cells in mice with

experimental allergic encephalomyelitis (EAE), and that immunization with a fragment of $V_\beta 8$ protects against induction of the disease (Howell et al., "Science" 3 November 1989, pp 668-670; Vandenbark et al., "Nature" 341:541-544 [1989]: and Offner et al., "J. Immun." 146:4165-4172 [1989]). Howell et al., WO 90/11294, published Oct. 4, 1990, teach vaccination with a TCR or a specified fragment of the TCR to treat autoimmune disorders. In particular, fragments from CDR2 were proposed as vaccine components. Offner et al., "Science" 251:430-432, 25 January 1991, disclose the ability to treat EAE with an intradermal or subcutaneous injection of TCR peptide in saline (without adjuvant) and suggest that this provides a feasible route for the eventual treatment of humans.

Howell et al. teach that human V_β 17 is closely associated with T cells active in RA and show the use of an alpha chain J segment in treatment of EAE (experimental autoimmune encephalomyelitis, a model for multiple sclerosis). Skibbens et al., WO 90/06758, published June 28, 1990, determined (example 11.2) that human V_β 3, 9 and 10 and V delta 1 were the TCRs most frequently expressed in rheumatoid synovial tissue-derived (expanded) T-cell lines, with $V_\beta 9$ being clearly dominant. One analysis showed that V_β 12 also was expressed more frequently, but Skibbens et al. evidently did not believe this TCR to be useful in the treatment of RA (specification pages 11 and 30; claims 85-88). Palliard et al., "Science" 253:241-352 (19 July 1991) implicated human V_β-14 bearing T cells in the pathology of RA. Also, according to Palliard et al., nearly all of these T cells used either J beta 1.1 or 2.3.

Vandenbark et al., WO 91/01133 (published 19 July 1990), contains disclosure relating to the screening of TCR peptides by DH response, administration of pharmaceutical compositions (anti-TCR and TCR compositions), and notes a bias to use of V beta 5.2 in humans in MS. On the other, Wucherpfenning et al., W0 91/15225 (published 17 October 1991) teach that MS in humans is linked to V beta 12 or 17.

It is an object of this invention to identify the preferentially used TCRs in human RA and to treat patients suffering from RA with compositions comprising V_β domains of such TCRs or antagonists thereto.

It is another object of this invention to identify those TCR J_β sequences which are to serve as targets for intervention in the treatment of RA or other autoimmune diseases in a given patient, using TCR sequences comprising such J_β sequences, or antibodies thereto.

It is a further object to provide novel compositions for the treatment of autoimmune disorders which comprise consensus and/or hybrid sequences of TCR domains amplified in such disorders.

Another object is to facilitate and simplify the diagnosis of TCR subdomain usage in an autoimmune disease.

Another object of this invention is to improve administration of the TCR or its fragments.

It is another object of this invention to provide improved methods for the diagnosis and treatment of RA and other autoimmune disorders.

Summary of the Invention

In accordance with the objects of this invention, RA is treated in human patients by administering a therapeutically effective amount of a polypeptide comprising an amino acid sequence of a human TCR V, J or C domain selected from the group of $V_\beta 7$, $V_\beta 8$, $V_\beta 12$, $V_\beta 13$, $V_\beta 14$, $V_\beta 15$, $J_\beta 2.1$, $J_\beta 2.2$, $V_\beta 2.3$, $J_\beta 2.5$, $J_\beta 2.7$ or $C_\beta 2$, or of an antibody capable of binding specifically to such sequence.

I have found that the TCR domains appearing with greatest frequency in RA patients share a great deal of amino acid sequence. In order to avoid the need to administer a tailored TCR domain for each patient, consensus or hybrid TCR domains are employed for patients having a given autoimmune disorder. In a preferred embodiment a "universal" J_β polypeptide family of consensus or hybrid sequences, and their amino acid sequence variants, are provided for the treatment of RA. These compounds have the structure

$A(Xaa1)_a(Xaa2)_b(Xaa3)_cPheGly(Xaa4)_1Gly(Xaa5)_1ArgLeu(Xaa6)_1Val(Xaa7)_cB$

(formula I; SEQ ID NO. 1)

wherein A is hydrogen, a sequence of about from 1 to 10 residues found in a TCR at the analogous site, a nonpeptidyl polymer, a non-TCR polypeptide, a TCR polypeptide selected from the group of a V beta 7, 8, 12, 13, 14 or 15 sequence, or a blocking group; Xaa1 is Glu or an amino acid residue having a hydroxy-substituted alkyl or hydroxy-substituted heteroalkyl side-chain; Xaa2 is Gln or an amino acid residue having a hydrophobic side-chain; Xaa3 is an amino acid residue having a cycloalkyl or hydroxy-substituted cycloalkyl side-chain; each of a, b and c are independently 1 or zero, provided that neither b nor c are zero if a is 1 and c is not zero if b is 1; Xaa4 is Pro or Glu; Xaa5 is an amino acid residue having a hydroxy-substituted alkyl or hydroxy-substituted heteroalkyl side-chain; Xaa6 and Xaa7 are independently an amino acid residue having a hydroxy-substituted alkyl, hydroxy-substituted heteroalkyl, alkyl or heteroalkyl side-chain; and B is the same as A except that hydrogen is hydroxy. In some embodiments the sequence of Formula I excludes the sequence of J beta 2.3.

In other embodiments of this invention, V beta consensus or hybrid sequences are designed by selecting residues from V beta 12, 13, 14, 15, 3, 7 and 8.

This invention also relates to methods for determining the specific V_β or J_β usage of T-cells in autoimmune diseases which does not require outgrowth of T-cells from affected tissue. The patient's T-cell population is screened by exposing the population to a bank of TCR polypeptides to identify the existence of T-cells that respond to each polypeptide. A T-cell proliferative response is taken as evidence of the existence of T-cells directed against T-cells bearing the test TCR, and therefore that such TCR-bearing T-cells are

targets for therapy. The peripheral T-cell population is assayed either in situ, for example by use of a multiple skin prick test using the bank of TCR polypeptides and observing for a DTH reaction or by use of an in vitro environment, e.g. by measuring the proliferative response in culture wells of the patient's peripheral blood T-cells (PBLs) to the TCR polypeptides.

This invention also relates to a method for treating T-cell mediated autoimmune conditions in a patient by administering a V_β polypeptide corresponding to a TCR expressed on clonally amplified T-cells (as determined by the method of this invention) in the patient or expressed on T-cells persistent at the site of inflammation. The J_β polypeptide for use in RA is set forth in Formula I. Other J and V_β domains preferentially used by T-cells in other autoimmune disorders such as those described supra are identified in the same fashion as is described herein for RA.

In another embodiment, treatment with the TCR or a domain thereof, e.g. a Vβ or a Jβ, is facilitated by simply administering a therapeutically effective dose of the TCR or its domain into the inflammatory lesion, e.g., the synovial fluid in RA, or directly into the vascular system - without using an immune adjuvant such as Freunds adjuvant or the like to stimulate the patient's response to the TCR or its selected subdomain. It was surprising that administration by these routes would be successful since it has been the practice heretofore to administer TCR domains in such a fashion as to elict a classical antigenic immune response, e.g. by use of an adjuvant or by subcutaneous administration, or both.

Brief Description of the Drawing

Fig. 1 illustrates the relative frequency of appearance of V beta usage in synovial infiltrating lymphocytes from RA patients.

Detailed Description of the Preferred Embodiments

Surprisingly, only a few clones of synovial T-cell TCR were found to be able to proliferate and survive in the presence of synovial tissue, and for the most part these clones are different from those identified by the art previously. It is believed that these TCR clones include the progeny of T-cells which are in fact responsible for the RA response, and that antagonism or anergy of these clones will ameliorate RA in the patient.

A suitable process for identifying preferential TCR use in RA or other autoimmune disorders comprises first obtaining a sample of synovium or other inflamed T-cell infiltrated tissue ("affected tissue") from the patient concerned. Typically, synovium samples are obtained at the time of joint replacement or other surgical procedures such as synovectomy involving an affected joint of the patient, although it is possible to obtain the samples by biopsy at the same time synovial fluid is expirated for analysis. The sample of the affected tissue is then placed in culture medium in the presence of IL-2 and the T-cells are allowed to proliferate from the tissue. Thereafter the proliferating T-cells are

transferred to culture in the presence of IL-2 and exposed to cross-linked antiCD3 antibodies every 7-10 days. They are grown until adequate amounts of T-cells are obtained for analysis. Any method for determining the TCR families in these cells is acceptable, for example, Southern blotting will determine clonal rearrangement of TCR. PCR analysis (using individual priming oligonucleotides capable of hybridizing only to one of the 14 families of J_β or the 24 families of V_β) is preferably used to identify the TCR domain (J_β or V_β) family member. Nucleic acid sequencing will confirm the identity of the specific V_β family member and serve as another means to determine J_β and C_β usage. Alternatively, individual priming oligonucleotides can be used to determine the TCR domain usage. A beta chain C domain primer is used as a control for the V_β or J_β assay. The PCR method is semiquantitative, and differs from that of the prior art (Skibbens et al., supra) in its treatment of background TCR usage. In the method of this invention the peripheral blood lymphocyte (PBL) usage of TCR regions is determined, but in a different fashion than that of the art. Here, the amount of mRNA or cDNA obtained in conventional fashion from PBLs from pooled blood (or from the individual patient being analyzed) is titered so that the quantity used is at the detectability threshold of the PCR amplification conditions to be employed in the affected tissue analysis. That is, under the conditions selected, the PCR analysis will not detect any peripheral TCR use but will detect at least one TCR domain in the affected tissue. Quite obviously, the titered amount of mRNA or cDNA to be used will vary depending upon the PCR conditions selected used, but this can be determined by routine methods. In contrast, the Skibbens et al. method laboriously amplifies each TCR domain from PBLs and from tissue and prepares a ratio of the degree of usage in tissue to that in PBLs for each TCR domain, and then identifies T-cell clones responsible for the autoimmune response on the basis of those possessing the highest numerical ratio of tissue: PBL usage. Accordingly, the method herein does not determine individual TCRs tissue PBL ratios. Stated differently the baseline control in the method of this invention is the highest relevant TCR domain (e.g. all V_β or J_β) usage in PBLs. As noted this difference produces more accurate results than those reported by Skibbens et al. and the method is much simpler to use in practice. The foregoing method is described in more detail in the examples below.

Alternatively, the RA patient's preferential Beta chain usage is determined by a DTH (Delayed Type Hypersensitivity) test using the otherwise conventional skin prick method with a bank of V_β and/or J_β polypeptides as set forth herein. Those polypeptides to which the patient exhibits a DTH response are administered to the patient for treatment of the patient's autoimmune disorder.

Alternatively, a (RA or other autoimmune disease) patient's peripheral blood T-cell proliferation response to a bank of V_β or J_β peptides may be used to determine the specific V_β or J_β peptides to be used for further treatment. In this alternative (which is the most convenient of three methods given here), PBLs from a peripheral source (e.g., blood from

the patient) are contacted in culture medium with a TCR or TCR domain polypeptide. Those TCRs or polypeptides that stimulate PBL growth are selected as candidate therapeutic agents for treating that patient. Normal donor PBLs (preferably from individuals who do not carry the MHC class I or II susceptibility determinants for RA or the autoimmune disease to be treated) are used as controls.

I have determined that among 16 patients with RA only a few TCR clones could be amplified from diseased tissue samples. These were V_β2(2), V_β3(5), V_β4(3), V_β7(6), V_β8(6), V_β9(1), V_β10(1), V_β12(8), V beta 13(8), V_β14(8), V_β15(5), V_β16(1), V beta 18(1), V_β19(1), V_β21(1), V_β22(1), and V_β23(1); these V_β's were found to be rearranged with a number of J beta domains as noted in Table III; J beta 2.3 and 2.7 appeared to be most preferentially used. Note: V_β14 is also designated V_β 3.3 in the literature; they have the same sequence. All patients used C_β2 with virtually each V beta (Table III). Most patients used more than one domain preferentially. Since some TCRs may have been derived from $CD8^+$ cells, subtraction of the contributions from these cells can be expected to remove some of the indicted TCRs from consideration, particularly those which are found in low frequency (1 or 2 instances). Further studies have demonstrated that the most prevalent V_β are V_β12 and 13, then V_β14 followed by V_β8, 7, 3 and 15. The remaining V_β's are found in minor proportions of patients.

Having identified the target TCR, several approaches can be used to antagonize the TCR-bearing T lymphocytes. In general, antagonists are either 1) the target TCR domain or a biologically active fragment thereof or 2) an antibody or receptor capable of specifically binding to and neutralizing the identified TCR domain.

It is possible to use an entire TCR beta chain containing one of the target V, J or C sequences, but is preferable to use an isolated domain of the TCR such as a J or V_β region or fragment thereof. The TCR polypeptides are synthesized by recombinant or in vitro methods using the known amino acid sequences of the domain in question. Preferably, the TCR domain sequence chosen is exactly that of the patient to be treated. However, since each TCR family (and particularly the V_β domains) includes a number of alleles, therapy is more convenient if the sequence chosen is a consensus sequence and thus does not represent the sequence of any naturally occurring domain per se. This may reduce the number of polypeptides in the therapeutic "bank". In general, the V_β polypeptide will contain the sequence of about residues 39-59 of the rat CDNA clone V_β510 (Vandenbark et al., Nature 341:541-544 [1988]) or to the rat VDJ2 sequence SSDSGNTE (SEQ.ID.2) OR ASSDSGNTE (SEQ.ID.3). Preferred for use herein are the V beta 7, 8, 12, 13, 14 or 15 sequences shown in Table I, together with their naturally occuring alleles falling within the same families.

TABLE I

V_β	PEPTIDE SEQUENCE	SEQ ID NO.
10	KLEESLKFLVYFQNEELIQ-KAEI	(SEQ ID NO. 4)
12	DPGHGLR-LIHYSYGVKDT-DKGE	(SEQ ID NO. 5)
13	DPGMGLR-LIHYSVGAGIT-DQGE	(SEQ ID NO. 6)
14	DPGLGLR-QIYYSMNVEVT-DKGD	(SEQ ID NO. 7)
15	DPGLGLR-LIYYSFDVKDI-NKGE	(SEQ ID NO. 8)
16	VMGKEIKFLLHFVKESKQD-ESGM	(SEQ ID NO. 9)
2	FPKQSLMLMATSNEGSKATYEQGV	(SEQ ID NO. 10)
3	DPGLGLR-LIYFSYDVKMK-EKGD	(SEQ ID NO. 11)
4	QPGQSLTLIATANQGSEATYESGF	(SEQ ID NO. 12)
7	KAKKPPELMFVYSYEKLSINES--	(SEQ ID NO. 13)
8	TMMRGLELLIYFNNNVPID-DSGM	(SEQ ID NO. 14)
9	DSKKFLKIMFSYNNKELIINET--	(SEQ ID NO. 15)
22	ILGQKVEFLVSFYNNEISE-KSEI	(SEQ ID NO. 16)
23	GPGQDPQFLISFYEKMQSD-KGSI	(SEQ ID NO. 17)

The sequences in Table I represent the CDR2 domains of the various human V_βs. The polypeptide antagonists for use in the therapy of RA are selected from within the V beta domains. They will contain about from 5 to 15 residues in most instances, but may constitute the entire CDR2 domain. Polypeptides of less than full V beta length shown in Table I generally will have N or C-terminal deletions of from 1 to about 5 resides. Examples of fragments are the series of fragments containing about from 6 to 12 residues, preferably about 10 residues, commencing at residue 1, 2, 3, 4, 5, or 6 of each V beta domain, in particular the V beta 7, 8, 13, 14 and 15 domains. Fragments ordinarily comprise the sequences DPG, LGL, RLI, YYS, YGV, KDT, DKG, PGL, GLR, LIY, YSY, GVK, DTD, KGE, GLG, LRL, IYY, SYG, VKD or TDK. V beta fragments optionally are fused to form inter-V beta hybrid domains, as is described more fully below. In addition, consensus sequences are derived from the autoimmune (particularly RA)-linked V beta sequences.

In preparing a consensus sequence, the residues selected for any site within the V beta sequence are, for RA, ranked on the basis of the frequency of usage as shown in Fig. 1, with the optimal residue being that which is shared at the given site by the greatest number of V beta sequences falling within the foregoing group. The same analysis is applied to other TCR V beta domains associated with other autoimmune disorders.

Hybrid V beta sequences comprise regions of about from 4 to 15 residues selected from at least 2 of each of the relevant V beta sequences. The component sequences used in the hybrid preferably are arranged in homologous order, e.g., for RA a exemplary hybrid would contain selected N-terminal sequence of V beta 13 fused at its C-terminus to the N-terminus of the residues making up the C-terminal domain of V beta 8 which is homologous to the remaining C-terminal residues of V beta 13. An exemplary hybrid comprises residues 1-6 of V beta 14 and residues 7-22 of V beta 7. In general, however, the hybrids will contain no less than about 7 residues of each V beta domain. It is also within the scope hereof to provide hybrids which contain more than 2 V beta sequences, and up to 5 or more, at least several of which are not homologously positioned. These

are more properly characterized as heteropolymeric V beta domains or fragments of V beta domains. The hybrid V beta sequences also optionally include consensus sequences.

In general, V beta consensus polypeptides intended for RA treatment (or components of hybrid sequences) comprise the following sequence of residues, from the N- to C-terminus (residues at each site are listed in order of preference; the sites are from Table I and are numbered from left to right of the sequences shown in Table I): 1: D, K, T; 2: P, A, M; 3: G, K, M; 4: L, H, M, K, R; 5: G, P; 6: L, P; 7: R, E; 8: -, L; 9: L, Q, M; 10: I, F; 11: Y, H, V; 12: Y, F; 13: S, N; 14: Y, V, M, N, F; 15: G, N, D, E; 16: V, A, K; 17: K, G, E, L, P; 18: I, D, V, S, M; 19: T, I, D, K; 20: -, N; 21: D, E, N; 22: K, S, Q; 23: G, -; 24: E, D, M, -; wherein the designation "-" means no residue, and wherein the polypeptide excludes the homologous sequence of human V beta 3. The polypeptide typically excludes the sequence of V beta 14 as well.

The V beta sequences herein, whether fragments, consensus sequences or hybrids, and whether or not the RA-linked TCR domains described above, have N- or C-terminii which are the same as A and B defined in Formula I. The V_β polypeptides optionally are covalently labelled as is described elsewhere herein for the J_β peptides.

In the compound of formula 1, A preferably is hydrogen and B is hydroxyl. However, the terminal portions of the compound are not believed to be important for biological activity and thus can be substituted with virtually any radical. Only substances which are clinically and unacceptably toxic to patients or which interfere with suppression of the target TCR-bearing T-cell clone preferably are not included with A or B, though it will be appreciated that such radicals can be present if the intended use for the polypeptide is as an in vitro diagnostic reagent. A or B also may be blocking groups usable in the in vitro synthesis of the polypeptides. A or B include nonpeptidyl polymers such as polysaccharides, polyethylene glycol, pluronic copolymers or other polyoxyalkylenes, or non-TCR polypeptides such as an antigen from a microbial or non-human animal source, an immunoglobulin chain (wherein the TCR polypeptide replaces a CDR, hypervariable region, Fv, Fc or fragment thereof), a receptor chain (replacing a transmembrane and/or cytoplasmic domain), a cytotoxic polypeptide such as ricin A chain, and the like. Polysaccharides include dextrans or other carbohydrates useful, for example, as matrices for insolubilization of the sequence for use in the purification of anti-TCR domain antibodies. In addition to the J beta domains associated with RA, the A or B groups are substituted onto other TCR fragments or domains associated with other autoimmune disorders.

Xaa1 may be either Glu or an amino acid residue having a hydroxy substituted side chain, e.g. Thr, Hydroxypro or Tyr. Generally, the side chain will be a hydroxy-substituted alkyl or hydroxy-substituted heteroalkyl group. The term "alkyl" or "heteroalkyl" means a radical comprising a linear, secondary or tertiary saturated alkyl group containing from 1 to about 10 carbon atoms and, optionally, one or more S or O heteroatoms (in the form of

esters or ethers, typically). In each instance, "amino acid residue" refers to the structure -(H)N-C(R)(H)-C(O)- wherein R is a side chain as noted.

Xaa2 generally is Gln or a amino acid residue having an alkyl side chain such as Leu. However, other hydrophobic residues such as those having aryl or alkyl aryl side chains can be employed, e.g. Phe.

Xaa3 is preferably Phe or Tyr. The cycloalkyl group is bonded to the alpha carbon directly or indirectly by alkyl of from 1 to 3 carbon atoms. The hydroxyl, if present, is generally in the para position.

None of Xaa1, Xaa2, Xaa3, Xaa4, Xaa5, Xaa6 or Xaa7 need to be naturally occurring amino acid residue, although it is preferable if they are.

Xaa4 is preferably Pro.

Xaa5 is a residue having a hydroxy substituted side chain, e.g. Thr, Hydroxypro or Tyr. Generally, the side chain will be a hydroxy-substituted linear, secondary or tertiary saturated alkyl group containing from 1 to about 10 carbon atoms and, optionally, one or more S or O heteroatoms (in form of esters or ethers, typically). Preferably, Xaa5 is Thr.

Xaa6 and Xaa7 preferably are Thr or Leu, although either also can be any residue having an alkyl, heteroalkyl, hydroxy-substituted alkyl or hydroxy substituted heteroalkyl side chain.

Xaa1, Xaa2, Xaa3, Xaa7 are not believed to critical and may be omitted, although Xaa3 and Xaa7 are preferentially present if any of these four residues is deleted.

The polypeptides are useful as diagnostic reagents. In labelled analogues, the J_β polypeptides of formula 1 or the V beta sequences are covalently substituted with fluorescent groups, chemiluminescent groups, haptens, radioisotopes, enzymes, stable free radicals and the like detectable functionalities. The N or C-termininus of the polypeptide is the preferred substitution site, although amino acid side chains alternatively may be covalently substituted with the detectable groups.

Antibodies capable of binding specifically to TCR domains and neutralizing their activity are known or may be prepared in conventional fashion. These antibodies are produced by hybridomas or recombinant host cell culture. The antibodies may be homologous to the patient, i.e., human antibodies are used with humans, or are derivatives of animal source antibodies, e.g. murine, antibodies such as chimeras, or CDR-grafted antibodies. In addition, the antibodies may be substituted with toxic moieties, e.g. the ricin A chain, or they may be in the form of polyvalent antibodies which are capable of binding other antigens, e.g. CD3, in addition to the target TCR. The IG class chosen preferably is IgG rather than IgD, IgA IgM or IgE. In addition, the IgG class optimally should be capable of binding complement and initiating ADCC. For the treatment of RA, the antibodies will be capable of specifically binding the V beta 7, 8, 12, 13, 14 or 15 sequences, J beta 2.1, 2.2, 2.3, 2.4, 2.5, 2.7 sequences, or C beta 2 sequences, and preferably, V beta 12, 13, 7, 8 or 15 and J beta 2.3 or 2.7. As in the case of TCR

fragments, a cocktail of antibodies having specificities for each target TCR domain is provided if desired, and heteropolyfunctional antibodies for multiple, different TCR domains also are within the scope hereof.

TCR antagonist polypeptides or antibodies are formulated into conventional pharmaceutical vehicles. In general, the formulations are sterile and isotonic and contain any substances needed to maintain the stability and activity of the antagonist.

For parenteral administration, the TCR antagonists or antibodies are formulated generally by mixing them at the desired degree of purity, in a unit dosage injectable form (solution, suspension, or emulsion), with a pharmaceutically acceptable carrier, i.e., one that is non-toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation. For example, the formulation preferably does not include oxidizing agents and other compounds that are known to be deleterious to polypeptides. It also is preferably free of immune adjuvants or stimulants, in particular Freunds adjuvant.

Generally, the formulations are prepared by contacting the TCR antagonists or antibodies uniformly and intimately with liquid carriers. Preferably the carrier is a parenteral carrier, more preferably a solution that is isotonic with the blood of the recipient. Examples of such carrier vehicles include water, saline, Ringer's solution, and dextrose solution. Non-aqueous vehicles such as fixed oils and ethyl oleate are also useful herein, as well as liposomes. Phosphate buffered saline or other isotonic buffers are preferable.

The carrier suitably contains minor amounts of additives such as substances that enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e.g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids, such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, mannose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; counterions such as sodium; and/or nonionic surfactants such as polysorbates, poloxamers, or PEG. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers may result in the formation of salts.

The TCR antagonist polypeptide or antibody to be used for therapeutic administration must be sterile. Sterility is readily accomplished by filtration through sterile filtration membranes (e.g., 0.2 micron membranes).

Therapeutic TCR antagonist polypeptide or antibody compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

TCR antagonist polypeptide or antibody ordinarily will be stored in unit or multi-dose containers, for example, sealed ampoules or vials, as an aqueous solution or as a lyophilized formulation for reconstitution. The initial consideration here must be that the carrier itself, or its degradation products, is nontoxic in the target tissue and will not further aggravate the disease. This can be determined by routine screening in animal models of the target disorder.

Heretofore TCR polypeptides have been administered so as to provoke an immune response by immunization with adjuvant or by subcutaneous administration. However, I have discovered that they may be administered without adjuvants and intravenously or intralesionally, and that immunostimulation is not necessary to achieve clinical improvement. If the products herein are used with adjuvants they may be fused to immunogenic polypeptides or haptens, or may be administered with a conventional adjuvant such as muramyl dipeptide, alum, a chemoattractant such as IL-8 or a cytokine such as TNF.

As a general proposition, the TCR antagonist or antibody is formulated and delivered at a dosage capable of inducing the suppressive or anergic immune response. Antibodies and polypeptides are formulated at concentrations compatible with physical integrity and consistent with convenient administration of a dosage by injection. Typically, the antagonist or polypeptide concentration will range about from 25 to 4,000 micrograms/ml, ordinarily 50 to 500 micrograms/ml and preferably 100 to 300 micrograms/ml.

The formulated, appropriate polypeptides or antibodies are administered to patients having autoimmune diseases. A candidate dosage to be used may be extrapolated from that which has been used previously in connection with the EAN model, in the case of humans taking into account the difference in pharmacokinetics between animals and humans. This means that the effective single iv. dose of 50 micrograms of V beta 8 polypeptide in the EAN rat (without adjuvant) which I have shown to be effective would extrapolate to approximately 2,000 micrograms in a human of typical 70 kg weight. Obviously, this dosage will be affected by the use of adjuvants, the stage of the autoimmune disorder, the potency of the polypeptide, the use of other therapies and other factors known to the skilled artisan. Similarly, the dosage of antibody also will be a matter to be determined by the clinician based on the affinity of the antibody for its TCR, the population of T cell clones bearing that TCR, the population of TCR on each clone, the stage of the autoimmune disorder, the use of other therapies (including a V beta or J beta polypeptide, at an earlier or later point in the therapy with antibody), and other factors known to the clinician. Typically, the dosage will be selected at a low level and gradually

increased until the desired therapeutic effect (decline in inflammation and other symptoms) is achieved.

The frequency of dosing will be dependent on the effective biological half life of the TCR antagonist and the duration of the subsequent immune response that ameliorates the disease process. Dosing frequency is readily determined by following the clinical condition of the patient or by assaying body fluids to detect deletion of the identified TCR-bearing lymphocytes if antibody is used or an elevated lymphocyte response in vivo or in vitro to the administered TCR peptides if TCR domains are used. This will be within the ordinary skill in the art. It is within the scope hereof to combine the TCR antagonist or antibody therapy with other novel or conventional therapies for autoimmune diseases. For example, the TCR antagonist or antibody therapy may be delivered in concert with other RA therapies, including bed rest, physical therapy, reconstructive joint surgery, application of heat, total lymphoid irradiation, synovectomy by irradiation with macroaggregates of ferric hydroxide labeled with a short-lived isotope (dysprosium-165) [Sledge et al., Arthritis Rheum., 29: 153-159 (1986); Vella et al., Arthritis Rheum., 31: 789-792 (1988)], supplemental icosapentaenoic and docosahexanoic acid, and drugs.

Examples of suitable cotreatment drugs (those used for treating RA) include nonsteroidal anti-inflammatory agents (drugs) such as aspirin, indomethacin, phenylbutazone, phenylacetic acid derivatives such as ibuprofen and fenoprofen, naphthalene acetic acids (naproxen), pyrrolealkanoic acid (tometin), indoleacetic acids (sulindac), halogenated anthranilic acid (meclofenamate sodium), piroxicam, zomepirac, and diflunisal; salicylates; anti-malarial agents such as hydroxychloroquine, sulfasalazine, gold colloids or salts, and penicillamine; immunosuppressive agents such as methotrexate and cyclosporine; intravenous methylprednisolone; cyclic oligosaccharides such as cyclodextrins, preferably in combination with a noninflammatory steroid such as cortexolone as described by Folkman et al., Science, 243: 1490-1493 (1989); antibodies against crucial components of the early phase of the immune response, including anti-Class II MHC antibodies [Gaston et al., Arthritis Rheum., 31: 21-30 (1988); Sany et al., Arthritis Rheum., 25: 17-24 (1982)], anti-interleukin-2 receptor antibodies [Kyle et al., Ann. Rheum. Dis., 48: 428-429 (1989)], anti-CD4 antibodies [Herzog et al., J. Autoimmun., 2: 627-642 (1989); Walker et al., J. Autoimmun., 2: 643-649 (1989)], and antithymocyte globulin [Shmerling and Trentham, Arthritis Rheum., 32: 1495-1496 (1989)]; antagonists such as antibodies to TNF-α or TNF-β; soluble receptors of TNF-α, TNF-β or IL-1; inhibitors of interleukin-1 [Herzog et al., Concepts Immunopathol., 7: 79-105 (1989)]; antibodies to CD11a, CD11b, CD11c, or CD18, and cytokines such as TGF-β [U.S. Pat. No. 4,806,523 issued Feb. 21, 1989; EP 269,408 published June 1, 1988], platelet-derived growth factor (PDGF) [Bonin and Singh, J. Biol. Chem., 263: 11052-11055 (1988)], interferon-gamma [Amento and Hayes, Clinical Res., 36: 599A (1988)],

as well as inhibitors of metalloproteinases, collagenase, stromalysin, inhibitors of metalloproteinase activation, or specific inducers of inhibitors of metalloproteinases such as MGSA/gro.

It is not necessary that such cotreatment drugs be included in the TCR antagonist compositions *per se*, although this may be convenient where such drugs are proteinaceous such as in the case of, e.g., γ-interferon, TGF-β, PDGF, and antibodies, including amino acid sequence variants. However, it is noted that proteins acting through different mechanisms may intervene at different points along the continuum of the immune disease process proteolytic enzyme cascade, so that the cytokines might be used in simultaneous treatment with the TCR antagonist or antibody or used earlier or later, depending on the nature and stage of the disease and the mechanism by which the particular cytokine operates.

The invention will be more fully understood by reference to the following example. They should not, however, be construed as limiting the scope of the invention.

Example I

Antibodies

T-cell activation was accomplished using the OKT3, an IgG2a mAB directed against CD3. For immunofluorescent staining, the following mABs were used at saturating concentrations; Leu 4 (CD3), Leu 3a (CD4), Leu 2a (CD8), Leu 18 (CD45RA), HLA-DR, TCR-1 (TCR $\alpha\beta$), and mouse IgG2 negative controls (Becton Dickinson, Mountain View, California); UCHL1 (CD45RO, Dakopatts, Denmark); TCR Δ1 (TCR $\gamma\Delta$), 1C1 (VB5), OT145 (VB6), 16G8 (VB8), and S511 (VB12, T-cell Sciences, Cambridge, MA); and PE conjugated goat anti mouse IgG (Caltag Laboratories, So. San Francisco, CA) for indirect staining.

Cell Culture Reagents

Complete medium consisted of RPMI 1640 (Gibco Laboratories, Grand Island, NY) supplemented with 10% heat inactivated fetal bovine serum. (Armour Pharmaceutical Co., Kanakee, IL), 1mM L-glutamine, 50 uM B-mercaptoethanol (Sigma Chemical Co., St. Louis, MO), and 100 U/ml penicillin/streptomycin (Gibco Labs, Grand Island, NY). Human rIL-2 was obtained from Genzyme (Boston MA) and used at 20 U/ml in complete media.

Culture and Expansion of T-cells

Rheumatoid synovial tissue samples from patients recently undergoing synovectomies or total joint replacements were cut into small pieces and immersed in complete medium and IL-2. The T-cells were allowed to expand until they became confluent, then were removed from the tissue culture, replated at $8x10^6$ cells/ml, and fed triweekly with fresh media and IL-2. See Example 9.1.3 of PCT WO 90/06758, *supra*. The T-cells were stimulated every 7 to 14 days by seeding them in plastic wells that had been precoated at 37°C for at least two hours with a 10 ug/ml solution of purified OKT3 (αCD3) in PBS (pH 7.4). After 48 hours, the cells were removed, washed, and replated at

$8x10^6$ cells/ml in fresh media and IL-2. The T-cell lines were analyzed by flow cytometry for surface antigen composition one to two weeks after removing them from the tissue, at which time each line was found to be greater than 95% positive for CD3 expression

DNA Extraction and Southern Blot Analysis

DNA was extracted from freshly harvested T-cells, subjected to enzymatic digestion, and electrophoresed through a 0.8% agarose gel. Samples were transferred to nitro-cellulose and hybridized according to Maniatis "Molecular Cloning" (Vol. 2, Sec. 9 [1989]). The TCR Cβ probe was obtained by using PCR; C-region primers in regions corresponding to the Eco RV and Hind III restriction sites amplified a 600 bp fragment from the constant region of JurB1 that was subcloned into a bluescript plasmid (pBS-).

PCR Analysis of TCR Beta Chain Variable Regions

Total T-cell RNA was extracted using RNAzol (Cinna/Biotecx, Friendswood, TX)

-cDNA was prepared from T-cell mRNA and amplified by PCR as described by, e.g., U.S. Patent No. 4,683,195 issued 28 July 1987; Mullin *et al.*, *Cold Spring Harbor Symp. Quant. Biol.*, **51**: 263 (1987); Erlich *et al.*, *PCR Technology*, (Stockton Press, NY 1989), and Erlich *et al.*, *Science*, **252**: 1643-1650 (1991).

-5' primers were designed to specify beta chain variable regions by family (see Table II).

-3' primer designated a constant region sequence common to all TCR beta chain transcripts.

-Control primers amplified a constant region sequence common to all TCR beta chain transcripts.

-Cycling parameters for thirty cycles: denature @ 95°C for 30 seconds, anneal primers @ 60°C for 30 seconds, polymerase extension @ 72°C for one minute.

Slot blot hybridization of PCR products

An aliquot of each PCR reaction was blotted onto nylon and hybridized overnight with a labelled C-region oligonucleotide (26-mer) that was designed to identify the constant region of the beta chain 5' t the original PCR constant region primer summarized in Table III.

The detection of low percentages of TCR usage by PCR was prevented by varying the amount of mRNA starting material until peripheral blood V_βs were barely detectable under the conditions of the given PCR reaction. A limited number of synovial V_βs then were readily detectable in comparison to those found in the background of peripheral blood, and determined by other analyses to represent V_β usage in the range of 12 to 50%. (see Table III).

TABLE II

Primer sequence used for PCR analysis of T cell receptor V_β gene usage in RA SILs.

Primer	cDNA/genomic clone	V_β-family members	Primer Sequence
$V_\beta 1$	PL5.2	1.1, 1.2	ACCAGGGCCTCCAGTTCCTCATTCAG (SEQ ID NO. 18)
$V_\beta 2$	PL2.13	2.1,2.2	CCGAAACAGAGTCTCATGCTGATGGC (SEQ ID NO. 19)
$V_\beta 3$	PL3.10	3.1,3.2	GAGATATTCCTGAGGGGTACAGTGTC (SEQ ID NO. 20)
$V_\beta 4$	PL2.14	4.1,4.2, 4.3	CAGAGCCTGACACTGATCGCAACTGC (SEQ ID NO. 21)
$V_\beta 5$	PL2.5	5.2,5.3	CCAGTTCCCTAACTATAGCTCTGAG (SEQ ID NO. 22)
$V_\beta 6$	PL5.10	6.2,-6.4, 6.6,6.7	GCTGCCCAACGATCGCTTCTTTGCAG (SEQ ID NO. 23)
$V_\beta 7$	PL4.9	7.1,7.2	GCTTCTCACCTGAATGCCCCAACAGC (SEQ ID NO. 24)
$V_\beta 8$	YT35	8.1,8.2, 8.4	CGTTCCGATAGATGATTCAGGGATGC (SEQ ID NO. 25)

TABLE II, cont.

Primer	cDNA/genomic clone	V_β-family members	Primer Sequence
V_β9	PL2.6	9.1	GAAACAGTTCCAAATCGCTTCTCACC (SEQ ID NO. 26)
V_β10	PL3.9	10.1,10.2	GTAAGAAGCTGGAAGAAGAGCTCAAG (SEQ ID NO. 27)
V_β11	PL3.12	11.1,11.2	CAGGAATGGAACTACACCTCATCCAC (SEQ ID NO. 28)
V_β12		12.2	GGGCTGAGGCTGATCCATTACTCA (SEQ ID NO. 29)
V_β13	PL4.24	12.3	GAGGCTGATTCATTACTCAGTTGGTG (SEQ ID NO. 30)
V_β14	PL8.1	3.3	GAGGTGACTGATAAGGGAGATGTTCC (SEQ ID NO. 31)
V_β15	ATL.21	15.1	AGGAGAGATCTCTGATGGATACAGTG (SEQ ID NO. 32)
V_β16	HBVT42	16.1	AGGATGAGTCCGGTATGCCCAACAAT (SEQ ID NO. 33)
V_β17	HBVTO2	17.1	GCTGAGATTGATCTACTACTCACAGA (SEQ ID NO. 34)
V_β18	PH29	18.1,18.2	CACAGTCATGTTTACTGGTATCGGCA (SEQ ID NO. 35)
V_β19	HBVT72	19.1	CGGAGATGCACAAGAAGCGATTCTCA (SEQ ID NO. 36)
V_β20	HUT	20.1	CATTGGTATTGACCAGATCAGCTCTG (SEQ ID NO. 37)
V_β21	IGRb01	21.1,21.2	TGGTGCAATCCTATATCTGGCCATGC (SEQ ID NO. 38)

TABLE II, cont.

Primer	cDNA/genomic clone	V_β-family members	Primer Sequence
V_β22	IGRb03	22	CATCAGGTCACACAGATGGGACAGGA (SEQ ID NO. 39)
V_β23	IGRb04	23	CTGATCGATTCTCAGCTCAACAGTTC (SEQ ID NO. 40)
V_β24	IGRb05	24	CATAACGTCATGTACTGGTACCAGCA (SEQ ID NO. 41)
C_β			TGTTCCCACCCGAGGTCGCTGTGTTT (SEQ ID NO. 42)

TABLE III

PATIENT	Vβ Family	Vβ SubFamily	Jβ	Cβ	Dβ	D&J TRANSLATION
RSL26						
	14	3.3	2.7	2	GCACCGGGATAC (SEQ ID NO. 43)	APGYYE**QYFGPGTRLTVT** (SEQ ID NO. 44)
	16	16.1	2.1	2	GCTAGCGGGACGTTTTAC (SEQ ID NO. 45)	RGTFYNE**QFFGPGTRLTVL** (SEQ ID NO. 46)
RSL27						
	7	7.2	2.7	2	CAGGACTCTGGGGG**GGGGGC**C (SEQ ID NO. 47)	QDSGGGAYE**QYFGPGTRLTVT** (SEQ ID NO. 48)
	12	12.2	2.5	2	CCCGGGGGA (SEQ ID NO. 49)	PGGET**QYFGPGTRLLVL** (SEQ ID NO. 50)
	13	12.4	2.3	2	CC**GACAG**TC (SEQ ID NO. 51)	PTVTDT**QYFGPGTRLTVL** (SEQ ID NO. 52)
RSL29						
	8	8	2.1	2	TTAGAGCCCGCAAGCGGGGTT (SEQ ID NO. 53)	LEPASGVYNE**QFFGPGTRLTVL** (SEQ ID NO. 54)
	10	10	2.7	2	AAAACCCAAGGGAGCTCC (SEQ ID NO. 55)	KTQGSSYE**QYFGPGTRLTVT** (SEQ ID NO. 56)
	12	-	2.2	2	GAACTCCCCGGGACATCG (SEQ ID NO. 57)	ELPGTSTGEL**FFGEGSRLTVL** (SEQ ID NO. 58)

TABLE III, cont.

PATIENT	Vβ Family	Vβ SubFamily	Jβ	Cβ	Dβ	D&J TRANSLATION
RSL30						
	8	8	2.3	2	TGGGCCCCTAACCCAGAGCCCGG (SEQ ID NO. 59)	WAPNPEPGRGT**QYFGPGTRLTVL** (SEQ ID NO. 60)
RSL31						
	2	2	2.3	2	CCTAGCGGGAGGCCC (SEQ ID NO. 61)	PRGRPTDT**QYFGPGTRLTVL** (SEQ ID NO. 62)
	2	4.1	2.7	2	GGGAAC (SEQ ID NO. 63)	GNNE**QYFGPGTRLTVT** (SEQ ID NO. 64)
	9	9.1	2.3	2	CAGCC**CAGGG**TGGGC (SEQ ID NO. 65)	QPRVGTDT**QYFGPGTRLTVL** (SEQ ID NO. 66)
	14	3.3	ND	2	not determined (ND)	
RSL32						
	2	2	2.7	2	GCC**GGGGGC**GAC (SEQ ID NO. 67)	AGGDYE**QYFGPGTRLTVT** (SEQ ID NO. 68)
	3	3.1	2.7	2	TCTCTTTTGG**GGGGGGG**AGGTCGCC (SEQ ID NO. 69)	SLLGGEVAYE**QYFGPGTRLTVT** (SEQ ID NO. 70)
	4	4.1	2.1	2	GC**TCAGG**CC (SEQ ID NO. 71)	AQAYE**QFFGPGTRLTVL** (SEQ ID NO. 72)
	12/13	12.3	2.2	2	TACGGTAGTGGGATTGGGTCGGCC (SEQ ID NO. 73)	YGSGIGSAGEL**FFGEGSRLTVL** (SEQ ID NO. 74)

TABLE III, cont.

PATIENT	Vβ Family	Vβ SubFamily	Jβ	Cβ	Dβ	D&J TRANSLATION
RSL33						
	8	8	2.5	2	TCCG**AGGGGGC**G (SEQ ID NO. 75)	SEGAT**QYFGPGTRLLVL** (SEQ ID NO. 76)
	15	15.1	2.1	2	GATTTGGGATCTCGGGCC (SEQ ID NO. 77)	**DLGSRANEQFFGPGTRLTVL** (SEQ ID NO. 78)
RSL34						
	4	4	2.1	2	GGACTAGCGGACTAC (SEQ ID NO. 79)	**LADYNEQFFGPGTRLTVL** (SEQ ID NO. 80)

NOTE: Except for the Vβ12 identified in patients RSL29 and RSL32, where the P is replaced by an E, FGPG RLTV is conserved in the Jβ subgroups we identified.

FG G L is conserved in all Jβs.

Analysis of an additional 4 RA patients showed the following V beta-J beta-C beta usage: SIL36: 12.2-2.2-2, 12.2-2.1-2, 15.1-2.7-2; SIL37: 8-2.5-2, 15-2.1-2, 15-2.3-2, 15-2.7-2; SIL46B: 3.1-2.3-2, 7.2-2.7-NA, 14.1-2.7-NA; SIL47B: 8-2.1-2, 8-2.2-2, 8-2.4-2, 8-2.5-2, 12.2-2.3-2, 12.2-2.7-2, 12.3-1.2-1, 12.3-2.1-2, 12.3-1.1-1, 12.4-2.7-2; SIL49: 14-2.2-2, 14-2.7-2, 15-2.1-2, 15-2.7-2. D beta usage was not restricted in these patients, in the same fashion as noted for the other patients above.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

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(ii) TITLE OF INVENTION: DIAGNOSING AND TREATING AUTOIMMUNE DISORDERS

(iii) NUMBER OF SEQUENCES: 80

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(A) MEDIUM TYPE: 5.25 inch, 360 Kb floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: patin (Genentech)

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER:
(B) FILING DATE: 23-SEP-1992
(C) CLASSIFICATION:

(vii) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER: 07/765222
(B) FILING DATE: 23-SEP-1991

(vii) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER: 07/779445
(B) FILING DATE: 18-OCT-1991

(vii) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER: 07/853362
(B) FILING DATE: 18-MAR-1992

(viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: Hensley, Max D.
(B) REGISTRATION NUMBER: 27,043
(C) REFERENCE/DOCKET NUMBER: 734P3

(ix) TELECOMMUNICATION INFORMATION:
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(C) TELEX: 910/371-7168

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 13 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

Xaa Xaa Xaa Phe Gly Xaa Gly Xaa Arg Leu Xaa Val Xaa
1 5 10 13

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Ser Ser Asp Ser Gly Asn Thr Glu
1 5 8

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

Ala Ser Ser Asp Ser Gly Asn Thr Glu
1 5 9

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Lys Leu Glu Glu Glu Leu Lys Phe Leu Val Tyr Phe Gln Asn Glu
1 5 10 15

Glu Leu Ile Gln Lys Ala Glu Ile
20 23

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

Asp Pro Gly His Gly Leu Arg Leu Ile His Tyr Ser Tyr Gly Val
1 5 10 15

Lys Asp Thr Asp Lys Gly Glu
20 22

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Asp Pro Gly Met Gly Leu Arg Leu Ile His Tyr Ser Val Gly Ala
1 5 10 15

Gly Ile Thr Asp Gln Gly Glu
20 22

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

Asp Pro Gly Leu Gly Leu Arg Gln Ile Tyr Tyr Ser Met Asn Val
1 5 10 15

Glu Val Thr Asp Lys Gly Asp
20 22

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Asp Pro Gly Leu Gly Leu Arg Leu Ile Tyr Tyr Ser Phe Asp Val
1 5 10 15

Lys Asp Ile Asn Lys Gly Glu
20 22

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

Val Met Gly Lys Glu Ile Lys Phe Leu Leu His Phe Val Lys Glu
1 5 10 15

Ser Lys Gln Asp Glu Ser Gly Met
20 23

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

Phe Pro Lys Gln Ser Leu Met Leu Met Ala Thr Ser Asn Glu Gly
1 5 10 15

Ser Lys Ala Thr Tyr Glu Gln Gly Val
20 24

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

Asp Pro Gly Leu Gly Leu Arg Leu Ile Tyr Phe Ser Tyr Asp Val

1 5 10 15

Lys Met Lys Glu Lys Gly Asp
20 22

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Gln Pro Gly Gln Ser Leu Thr Leu Ile Ala Thr Ala Asn Gln Gly
1 5 10 15

Ser Glu Ala Thr Tyr Glu Ser Gly Phe
20 24

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

Lys Ala Lys Lys Pro Pro Glu Leu Met Phe Val Tyr Ser Tyr Glu
1 5 10 15

Lys Leu Ser Ile Asn Glu Ser
20 22

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

Thr Met Met Arg Gly Leu Glu Leu Leu Ile Tyr Phe Asn Asn Asn
1 5 10 15

Val Pro Ile Asp Asp Ser Gly Met
20 23

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

Asp Ser Lys Lys Phe Leu Lys Ile Met Phe Ser Tyr Asn Asn Lys
1 5 10 15

Glu Leu Ile Ile Asn Glu Thr
20 22

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 23 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION. SEQ ID NO:16:

Ile Leu Gly Gln Lys Val Glu Phe Leu Val Ser Phe Tyr Asn Asn
1 5 10 15

Glu Ile Ser Glu Lys Ser Glu Ile
20 23

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

Gly Pro Gly Gln Asp Pro Gln Phe Leu Ile Ser Phe Tyr Glu Lys
1 5 10 15

Met Gln Ser Asp Lys Gly Ser Ile
20 23

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

ACCAGGGCCT CCAGTTCCTC ATTCAG 26

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

CCGAAACAGA GTCTCATGCT GATGGC 26

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

GAGATATTCC TGAGGGGTAC AGTGTC 26

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

CAGAGCCTGA CACTGATCGC AACTGC 26

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

CCAGTTCCCT AACTATAGCT CTGAG 25

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

GCTGCCCAAC GATCGCTTCT TTGCAG 26

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

GCTTCTCACC TGAATGCCCC AACAGC 26

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 bases

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION. SEQ ID NO:25:

CGTTCCGATA GATGATTCAG GGATGC 26

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

GAAACAGTTC CAAATCGCTT CTCACC 26

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

GTAAGAAGCT GGAAGAAGAG CTCAAG 26

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

CAGGAATGGA ACTACACCTC ATCCAC 26

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

GGGCTGAGGC TGATCCATTA CTCA 24

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

GAGGCTGATT CATTACTCAG TTGGTG 26

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

GAGGTGACTG ATAAGGGAGA TGTTCC 26

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

AGGAGAGATC TCTGATGGAT ACAGTG 26

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

AGGATGAGTC CGGTATGCCC AACAAT 26

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

GCTGAGATTG ATCTACTACT CACAGA 26

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

CACAGTCATG TTTACTGGTA TCGGCA 26

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

CGGAGATGCA CAAGAAGCGA TTCTCA 26

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

CATTGGTATT GACCAGATCA GCTCTG 26

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

TGGTGCAATC CTATATCTGG CCATGC 26

(2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

CATCAGGTCA CACAGATGGG ACAGGA 26

(2) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

CTGATCGATT CTCAGCTCAA CAGTTC 26

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

CATAACGTCA TGTACTGGTA CCAGCA 26

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

TGTTCCCACC CGAGGTCGCT GTGTTT 26

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

GCACCGGGAT AC 12

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

Ala Pro Gly Tyr Tyr Glu Gln Tyr Phe Gly Pro
1 5 10

Thr Val Thr
18

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

GCTAGCGGGA CGTTTTAC 18

(2) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

Arg Gly Thr Phe Tyr Asn Glu Gln Phe Phe Gly
1 5 10

Leu Thr Val Leu
19

(2) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

CAGGACTCTG GGGGGGGGGC C 21

(2) INFORMATION FOR SEQ ID NO:48:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

Gln Asp Ser Gly Gly Gly Ala Tyr Glu Gln Tyr Phe Gly Pro Gly
1 5 10 15

Thr Arg Leu Thr Val Thr
20 21

(2) INFORMATION FOR SEQ ID NO:49:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

CCCGGGGGA 9

(2) INFORMATION FOR SEQ ID NO:50:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

Pro Gly Gly Glu Thr Gln Tyr Phe Gly Pro Gly Thr Arg Leu Leu
1 5 10 15

Val Leu
17

(2) INFORMATION FOR SEQ ID NO:51:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

CCGACAGTC 9

(2) INFORMATION FOR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

Pro Thr Val Thr Asp Thr Gln Tyr Phe Gly Pro Gly Thr Arg Leu
1 5 10 15

Thr Val Leu
16

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

TTAGAGCCCG CAAGCGGGGT T 21

(2) INFORMATION FOR SEQ ID NO:54:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

Leu Glu Pro Ala Ser Gly Val Tyr Asn Glu Gln Phe Phe Gly Pro
1 5 10 15

Gly Thr Arg Leu Thr Val Leu
20 22

(2) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

AAAACCCAAG GGAGCTCC 18

(2) INFORMATION FOR SEQ ID NO:56:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

Lys Thr Gln Gly Ser Ser Tyr Glu Gln Tyr Phe Gly Pro Gly Thr
1 5 10 15

Arg Leu Thr Val Thr
20

(2) INFORMATION FOR SEQ ID NO:57:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

GAACTCCCCG GGACATCG 18

(2) INFORMATION FOR SEQ ID NO:58:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

Glu Leu Pro Gly Thr Ser Thr Gly Glu Leu Phe Phe Gly Glu Gly
1 5 10 15

Ser Arg Leu Thr Val Leu
20 21

(2) INFORMATION FOR SEQ ID NO:59:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:

TGGGCCCCTA ACCCAGAGCC CGG 23

(2) INFORMATION FOR SEQ ID NO:60:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:

Trp Ala Pro Asn Pro Glu Pro Gly Arg Gly Thr Gln Tyr Phe Gly
1 5 10 15

Pro Gly Thr Arg Leu Thr Val Leu
20 23

(2) INFORMATION FOR SEQ ID NO:61:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:

CCTAGCGGGA GGCCC 15

(2) INFORMATION FOR SEQ ID NO.62.

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:

Pro Arg Gly Arg Pro Thr Asp Thr Gln Tyr Phe Gly Pro Gly Thr
1 5 10 15

Arg Leu Thr Val Leu
20

(2) INFORMATION FOR SEQ ID NO:63:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:

GGGAAC 6

(2) INFORMATION FOR SEQ ID NO:64:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:

Gly Asn Asn Glu Gln Tyr Phe Gly Pro Gly Thr Arg Leu Thr Val
1 5 10 15

Thr
16

(2) INFORMATION FOR SEQ ID NO:65:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:

CAGCCCAGGG TGGGC 15

(2) INFORMATION FOR SEQ ID NO:66:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 amino acids

(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

Gln Pro Arg Val Gly Thr Asp Thr Gln Tyr Phe Gly Pro Gly Thr
1 5 10 15

Arg Leu Thr Val Leu
20

(2) INFORMATION FOR SEQ ID NO:67:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:67:

GCCGGGGGCG AC 12

(2) INFORMATION FOR SEQ ID NO:68:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:

Ala Gly Gly Asp Tyr Glu Gln Tyr Phe Gly Pro Gly Thr Arg Leu
1 5 10 15

Thr Val Thr
18

(2) INFORMATION FOR SEQ ID NO:69:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:

TCTCTTTTGG GGGGGGAGGT CGCC 24

(2) INFORMATION FOR SEQ ID NO:70:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:70:

Ser Leu Leu Gly Gly Glu Val Ala Tyr Glu Gln Tyr Phe Gly Pro
1 5 10 15

Gly Thr Arg Leu Thr Val Thr
20 22

(2) INFORMATION FOR SEQ ID NO:71:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:71:

GCTCAGGCC 9

(2) INFORMATION FOR SEQ ID NO:72:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:72:

Ala Gln Ala Tyr Glu Gln Phe Phe Gly Pro Gly Thr Arg Leu Thr
1 5 10 15

Val Leu
17

(2) INFORMATION FOR SEQ ID NO:73:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:73:

TACGGTAGTG GGATTGGGTC GGCC 24

(2) INFORMATION FOR SEQ ID NO:74:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:74:

Tyr Gly Ser Gly Ile Gly Ser Ala Gly Glu Leu Phe Phe Gly Glu
1 5 10 15

Gly Ser Arg Leu Thr Val Leu
20 22

(2) INFORMATION FOR SEQ ID NO:75:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 bases
(B) TYPE: nucleic acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:75:

TCCGAGGGGG CG 12

(2) INFORMATION FOR SEQ ID NO:76:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:76:

Ser Glu Gly Ala Thr Gln Tyr Phe Gly Pro Gly Thr Arg Leu Leu
1 5 10 15

Val Leu
17

(2) INFORMATION FOR SEQ ID NO:77:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:77:

GATTTGGGAT CTCGGGCC 18

(2) INFORMATION FOR SEQ ID NO:78:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:78:

Asp Leu Gly Ser Arg Ala Asn Glu Gln Phe Phe Gly Pro Gly Thr
1 5 10 15

Arg Leu Thr Val Leu
20

(2) INFORMATION FOR SEQ ID NO:79:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 bases
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:79:

GGACTAGCGG ACTAC 15

(2) INFORMATION FOR SEQ ID NO:80:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:80:

Leu Ala Asp Tyr Asn Glu Gln Phe Phe Gly Pro Gly Thr Arg Leu
1 5 10 15

Thr Val Leu
18

What is claimed is:

1. A composition comprising a compound having the structure

$A(Xaa1)_a(Xaa2)_b(Xaa3)_cPheGly(Xaa4)_1Gly(Xaa5)_1ArgLeu(Xaa6)_1Val(Xaa7)_cB$

(formula I; SEQ ID NO.1)

wherein A is hydrogen, a flanking sequence of about from 1 to 10 residues found in a TCR at the analogous site, a nonpeptidyl polymer, a non-TCR polypeptide, a TCR polypeptide selected from the group of a V beta 7, 8, 12, 13, 14 or 15 sequence, or a blocking group; Xaa1 is Glu or an amino acid residue having a hydroxy-substituted alkyl or hydroxy-substituted heteroalkyl side-chain; Xaa2 is Gln or an amino acid residue having a hydrophobic side-chain; Xaa3 is an amino acid residue having a cycloalkyl or hydroxy-substituted cycloalkyl side-chain; each of a, b and c are independently 1 or zero, provided that neither b nor c are zero if a is 1 and c is not zero if b is 1; Xaa4 is Pro or Glu; Xaa5 is an amino acid residue having a hydroxyl-substituted alkyl or hydroxy-substituted heteroalkyl side-chain; Xaa6 and Xaa7 are independently an amino acid residue having a hydroxy-substituted alkyl, hydroxy-substituted heteroalkyl, alkyl or heteroalkyl side-chain; and B is hydroxy, a flanking sequence of about from 1 to 10 residues found in a TCR at the analogous site, a nonpeptidyl polymer, a non-TCR polypeptide, a TCR polypeptide selected from the group of a V beta 7, 8, 12, 13, 14 or 15 sequence, or a blocking group.

2. The composition of claim 1 wherein a, b, c, and d are zero and the sequence excludes the sequence of any T cell receptor D region or V beta region.

3. The composition of claim 2 wherein Xaa4 is Pro and Xaa5 is Thr or Ser.

4. The composition of claim 3 wherein Xaa5 is Thr.

5. The composition of claim 1 wherein A is hydrogen and B is hydroxyl.

6. The composition of claim 1 which is labelled with a detectable group.

7. The composition of claim 6 wherein the detectable group is a fluorescent group, a chemiluminescent group, a hapten, a radioisotope, an enzyme, a stable free radical, or an antigen.

8. The composition of claim 1 wherein A or B is a nonpeptidyl polymer.

9. The composition of claim 8 wherein the nonpeptidyl polymer is a polysaccharide.

10. A composition comprising a T-cell receptor consensus or hybrid J or V beta domain.

11. The composition of claim 10 wherein the consensus or hybrid is that of a V beta domain and comprises sequence from V beta 7, 8, 12, 13, 14 or 15.

12. The composition of claim 11 comprising the sequences DPG, LGL, RLI, YYS, YGV, KDT, DKG, PGL, GLR, LIY, YSY, GVK, DTD, KGE, GLG, LRL, IYY, SYG, VKD or TDK.

13. A method or treating an autoimmune disorder in a patient comprising administering to the patient a therapeutically effective dose of a composition comprising a T cell receptor consensus or hybrid J or V beta domain

14. A method for treating rheumatoid arthritis comprising administering to a human patient a therapeutically effective amount of a polypeptide comprising a sequence from the human T-cell receptor V_β-7, -8, -12, -13, -14, or -15 domain, J_β-2.1, -2.2, -2.3, -2.5 or -2.7 domain, or C beta 2 domain, or an antibody capable of binding to the sequence.

15. The method of claim 14 wherein the human T-cell receptor sequence corresponds to the sequence of about residues 39-59 of the rat cDNA clone Vβ510 or the sequence corresponding to the rat VDJ sequence SSDSGNTE (SEQ ID NO. 2) or ASSDSGNTE (SEQ ID NO. 3).

16. The method of claim 14 wherein the sequence is a consensus or hybrid T-cell receptor V beta sequence.

17. The method of claim 14 wherein the sequence is a hybrid receptor comprising at least 2 T-cell receptor V beta sequences.

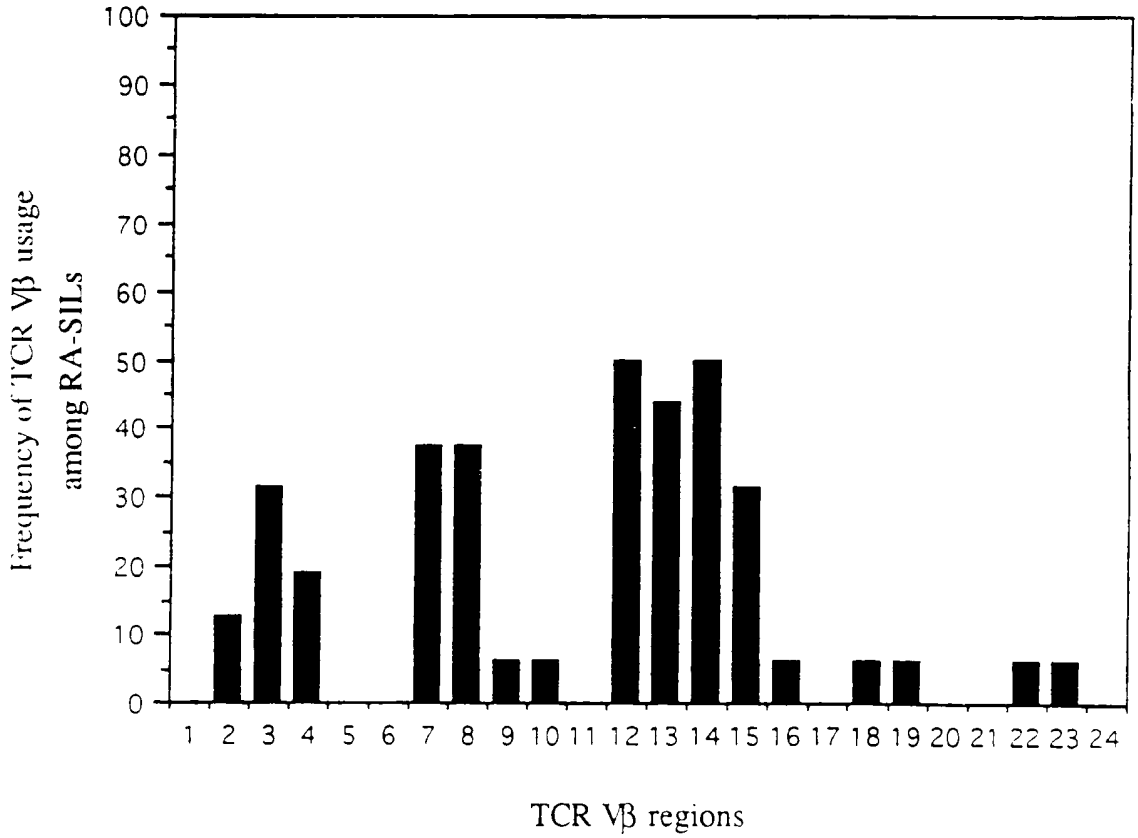
18. The method of claim 14 wherein the polypeptide sequence contains at least 5 residues and is comprised within the V beta-7, -8, -12, -13, -14 or -15 sequences of Table 1.

19. A method for treating a T-cell mediated autoimmune disease in a patient comprising intravenously or intralesionally administering a T-cell receptor polypeptide to the patient in the absence of an agent for stimulating the patient to recognize the polypeptide as an antigen.

20. A method for identifying a T-cell receptor associated with a T-cell mediated autoimmune disease in a patient, comprising removing a sample of T-cells from the patient culturing the cells in vitro in contact with a TCR polypeptide, and observing for accelerated proliferation or activation of the T-cells in the presence of the polypeptide.

21. A method for identifying a T-cell receptor associated with RA in a patient, comprising administering a plurality of candidate T-cell receptor polypeptides to the skin of the patient and observing for the development of a DTH response at any site of exposure to a polypeptide.

FIG. 1


Frequency of TCR Vβ usage among RA-SILs
100
90
80
70
60
50
40
30
20
10
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
TCR Vβ regions

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 92/08094

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)°

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07K15/06; A61K37/02; A61K39/395; G01N33/68

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07K ; A61K ; G01N

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	WO,A,9 101 133 (A. VANDENBARK) 7 February 1991 cited in the application	10-18,20
Y	see claims	1-7
Y	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE USA vol. 82, no. 24, December 1985, WASHINGTON DC, US pages 8624 - 8628 B. TOYONAGA ET AL. 'Organization and sequences of the diversity, joining, and constant region genes of the human T-cell receptor beta chain.' see abstract; figures 3,4	1-7

-/--

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
12 JANUARY 1993	29. 01. 93
International Searching Authority: EUROPEAN PATENT OFFICE	Signature of Authorized Officer: NOOIJ F.J.M.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	WO,A,9 109 623 (CALIFORNIA INSTITUTE OF TECHNOLOGY) 11 July 1991 see claims	10-12, 14,16-18
X	WO,A,9 011 294 (THE IMMUNE RESPONSE CORPORATION) 4 October 1990 see claims	10,13, 14, 16-18,20
A	ARTHRITIS AND RHEUMATISM vol. 34, no. 9SUP, September 1991, NEW YORK, USA page S39 E. AMENTO ET AL. 'Limited T cell receptor Vbeta usage in rheumatoid synovial tissue.' see abstract 40	1-12

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Arucle 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 19, 21
because they relate to subject matter not required to be searched by this Authority, namely:
see PCT-Rule 39.1(iv)
remark: Although claims 13-18 are directed to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventuons in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort jusufying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invenuon first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

US 9208094
SA 65239

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 12/01/93
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9101133	07-02-91	AU-A-	6048590	22-02-91
		CA-A-	2064077	20-01-91
WO-A-9109623	11-07-91	AU-A-	7347091	24-07-91
		EP-A-	0506893	07-10-92
WO-A-9011294	04-10-90	AU-A-	5356790	22-10-90
		EP-A-	0463101	02-01-92
		JP-T-	4506512	12-11-92